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Asymmetric cyclopropanation in Ionic Liquids promoted by dicopper complexes of ditopic ligands

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Enantioselective catalysis – Biphasic catalysis – Recoverable catalyst – Ditopic chiral ligand – Copper – Ionic liquid

Abstract

The use of ionic liquid phases to immobilise dicopper complexes of ditopic chiral ligands bearing bis(oxazoline) moieties is explored in the enantioselective cyclopropanation reaction of styrene with ethyl diazoacetate. Recoverability of these catalytic phases is studied using different ionic liquids and ligands. The origin of the ionic liquid is determinant both for the catalytic results and the reusability of the system.

1. Introduction

Enantioselective reactions promoted by chiral metal complexes is an important topic in chemical research, both from academic and industrial points of view.[1,2] In this regard, bis(oxazolines) (Box) are versatile chiral ligands that are able to form complexes with

different metals, which catalyse a variety of organic reactions.[3,4] The immobilisation of these complexes, using a large variety of strategies, allows obtaining recoverable catalysts for a wide range of organic reactions.[5–7]

An enantioselective catalysts recycling strategy, usually used with metal complexes of chiral ligands, consists in the use ionic liquids phases. In most cases, the catalytic complex remains dissolved in the IL, whereas the reaction products are removed from this phase by extraction with a suitable solvent. Some examples of application of this strategy using chiral Box-copper complexes as catalysts in Diels–Alder,[8] hetero-Diels–Alder[9] or glyoxylate-ene reactions[10] have been published by Kim and co-workers.

One of the problems with this kind of catalyst immobilisation is the possibility of partial extraction of the chiral ligand during the reaction work-up. This would lead to the presence of non-chiral metal centres in the recycled IL phase, still able to catalyse the reaction, but in a non-enantioselective manner. Some strategies have been tested to minimise ligand leaching. The most obvious is to use more coordinating ligands, so the coordination equilibrium remains shifted towards the metal complex at any circumstance.[11] Another possibility is to modify the chiral ligand by binding it one or more ionic moieties. For instance, imidazolium-tagged chiral Box have been used by Zhou and co-workers to prepare recyclable copper complexes, subsequently employed to catalyse Diels–Alder[12] and Henry reactions.[13,14]

Very recently, we have described the synthesis of several ditopic chiral ligands based on the azabis(oxazoline) (**2a** and **2b**) and bis(oxazoline) units (**2c**-**2f**) (Figure 1). These ligands have been applied to the preparation of copper coordination polymers in order to promote several organic reactions, such as cyclopropanation of alkenes with ethyl diazoacetate,[15–17] nitroaldol (Henry) reaction,[18] and allylic oxidation of cycloalkenes with peroxoesters.[19,20] In all cases the catalyst can be recovered following a *release-and-capture* strategy, since the coordination

polymer, which is disassembled in the reaction media, can be precipitated after the reaction end, and then easily separated from reagents and reaction products by decantation.

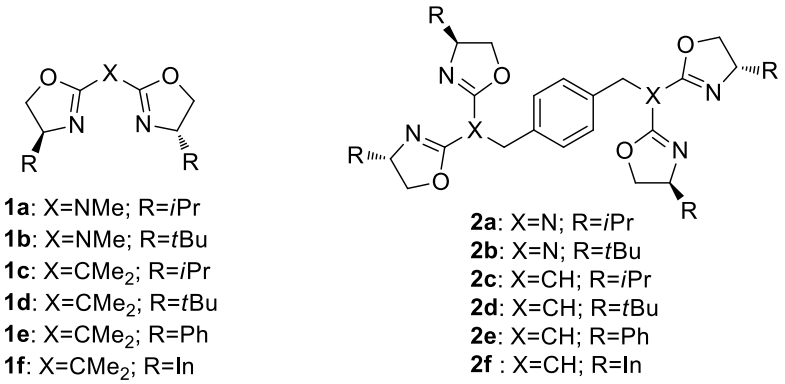
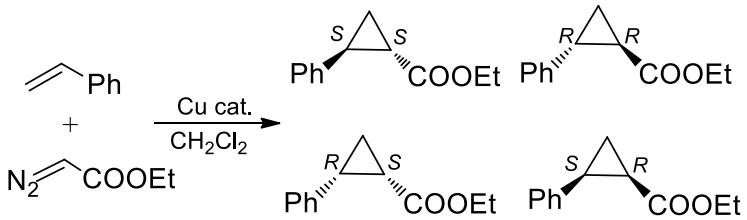


Figure 1. Structure of the different chiral ligands used in this work.

These kinds of ditopic chiral ligands offer a third option to minimise ligand leaching from IL phases, namely the use double metal-ligand complexes as catalysts.[21] The existence of two consecutive coordination equilibria would decrease the presence of free ligand in solution. With this hypothesis in mind, we undertook the study of the asymmetric cyclopropanation reaction in ionic liquids with copper complexes of ditopic ligands as catalysts. Thus, in this work, we report the use of several monotopic and ditopic bis(oxazoline) (Box) and azabis(oxazoline) (Azabox) based ligands (Figure 1) complexed with copper, immobilised in ionic liquids (IL), and their use as promoters of the equimolecular enantioselective cyclopropanation reaction between styrene and ethyl diazoacetate (Scheme 1), with particular interest in catalyst recycling issues.



Scheme 1. Cyclopropanation reaction between styrene and ethyl diazoacetate.

2. Results and Discussion

2.1. Catalysis in [EMIM][OTf]

The best results obtained for cyclopropanation reactions with a catalyst immobilised in an ionic liquid phase were achieved with the *t*BuAzabox-copper and *t*BuBox-copper complexes dissolved in [EMIM][OTf] (1-ethyl-3-methylimidazolium triflate), and were reported by our research group some years ago.[11] The new *t*BuDax and *t*BuDiBox ligands, which join together two *t*BuAzabox or *t*BuBox moieties, were expected to be successful in biphasic catalysis with ionic liquids, too.

The copper salt used in cyclopropanation reaction is vital, the use of chloride as the counterion in cyclopropanation reactions carried out in molecular solvents leading to much worse results,[22] due to the influence of the counterion on the geometry of the transition state.[23] However, it has been proved that in ionic liquids the anion of the ionic liquid plays the role of counterion and therefore, the selectivity and enantioselectivity results are the same with CuCl and with $Cu(OTf)_2$.[11] In addition, in the case of using CuCl,, the yield improves because no ethyl diazoacetate is consumed in the *in situ* reduction of copper. Therefore, in previous works this copper salt was used achieving good results, because of that, throughout this work the complexes with CuCl will be used as catalysts.[11,24]

The first step was to try to reproduce the good results obtained in the previous works. We started using the *t*BuBox-CuCl complex due to the commercial availability of this chiral ligand. The results obtained when we tried to emulate exactly experimental conditions previously reported are shown in Table 1, entry 2. When they are compared with the previously reported results (entry 1), it can be seen that both yield and enantioselectivity are considerably worse. This could be due to the presence of free copper, since the complex had not been prepared previously to its dissolution in the IL phase. To test this possibility we decided to change the catalyst preparation by synthesising the complex in a previous step, and the corresponding results are shown in Table 1, entry 3. Although these results represent a

significant improvement with regard to the previous ones, doubling over both yield and enantioselectivity values, they are still worse than those previously reported using the same conditions.

Table 1
Cyclopropanation reactions between styrene and ethyl diazoacetate catalysed by *t*BuBox-CuCl (**1d-Cu**) in [EMIM][OTf].[a]

Entry	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1[b]	51	73/27	85	78
2[c]	18	72/28	34	36
3[d]	29	72/28	68	72
4[e]	24	74/26	58	57
5[f]	20	72/28	34	38
6[g]	19	72/28	44	45

[a] Reagents and conditions: styrene (1 equiv.), ethyl diazoacetate (1 equiv.), L*-CuCl (1 mol%), [EMIM][OTf] 0.5 mL previously dried in presence of P_2O_5, room temperature, 20 h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1*R*,2*R*)-*trans*-cyclopropane and (1*R*,2*S*)-*cis*-cyclopropane are the major isomers. [b] Taken from ref. [11] Cu(OTf) was used as copper salt. [c] Without a previous preparation of the catalytic complex in CH_2Cl_2. [d] Previous preparation of the catalytic complex in CH_2Cl_2. [e] $Cu(OTf)_2$ was used as copper salt. [f] No drying treatment was applied to the IL prior use. [g] IL was also dried over Na_2SO_4 prior to use.

The main difference between the previous and present experimental conditions was the origin of the IL used. The [EMIM][OTf] used in the previous works was synthesised in the Prof. Vaultier´s laboratories at the University of Rennes I (France), whereas that used in the present work was commercial. As it have been already reported, the presence of halides in the ionic liquid may result in significant declining results.[22] We tried to prove the presence of halides in the commercial IL by adding a silver salt, but the results were not relevant; we did not appreciate the appearance of the typical white precipitate owing to the formation of AgX. As we were using CuCl, which is a halide source, we carried out a test avoiding the chloride salt, using $Cu(OTf)_2$ instead (Table 1, entry 4). The results of this test were not satisfactory either. Finally, we checked the possible influence of the presence of water in the ionic liquid. In all cases, IL had been previously dried under vacuum in the presence of P_2O_5. This time, two tests were carried out (Table 1, entries 5 and 6), one without doing any previous drying treatment to the IL, and the other with a thorough drying treatment over Na_2SO_4. No

improvement of the results was observed with the completely anhydrous IL, so we were not able to identify the origin of the difference present in the commercial IL that makes the results worse.

In spite of the moderate results obtained using the commercial IL, and in order to prove the recoverability capacity of the complexes with the ditopic ligands immobilised in IL, we carried out the title reaction with DiBox-CuCl and DAX-CuCl complexes. The recycling of the catalyst was performed by adding *n*-hexane at the end of the reaction; products and by-products were extracted in this liquid phase, so after removing the hexane phase, the IL phase containing the catalyst was ready for a next run. When the complexes with the ditopic ligands are used, two equivalents of copper salt (CuCl) were added per ligand equivalent, leading to a bis-metal complex (Figure 2). In this case the previous preparation of the complex in CH_2Cl_2 was not carried out. The metal salt and the chiral ligand were directly weighted in the reaction tube and the IL, previously dried in the presence of P_2O_5, was subsequently added.

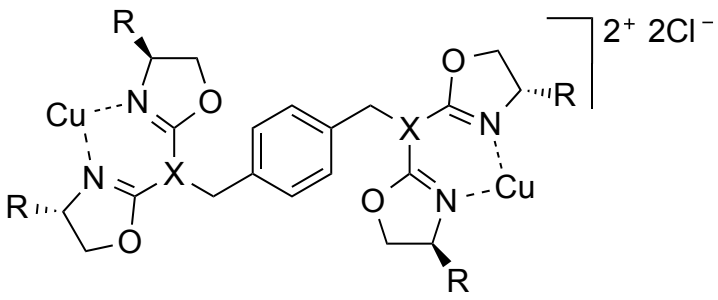


Figure 2. Structure of the complexes ditopic ligand-CuCl.

In all graphs presented henceforth, only the enantioselectivity of the *trans*-cyclopropanes will be presented, since it is the most representative of the performance of the catalytic system and is much easier to compare than the reaction yield.

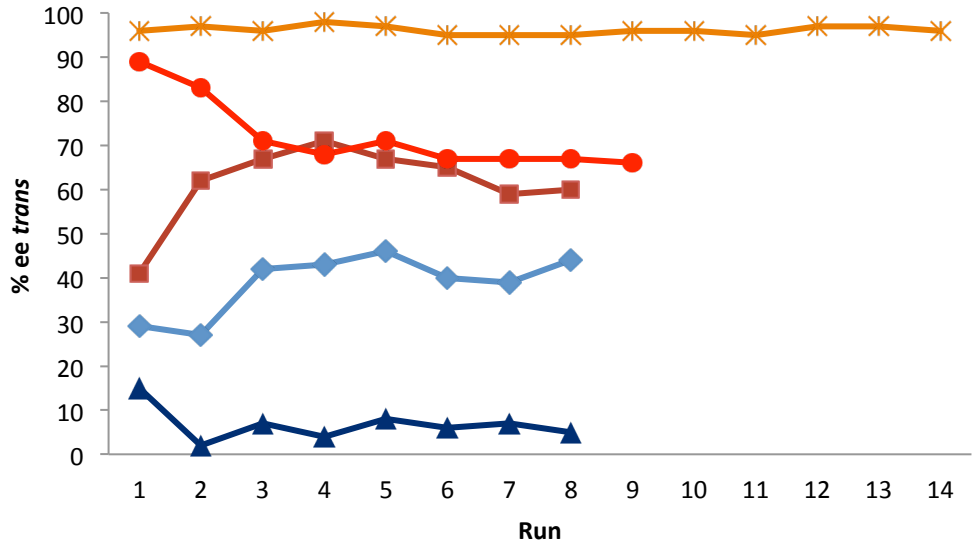


Figure 3. Recycling experiments with the complexes L*-CuCl immobilised in [EMIM][OTf]. In commercial [EMIM][OTf], L*= *i*PrDiBox **2c** (◆), *t*BuDiBox **2d** (■), *i*PrDAX **2a** (▲), *t*BuDAX **2b** (●). In synthesised [EMIM][OTf], L*= *t*BuDAX **2b** (✳).

Figure 3 displays the catalytic results obtained in successive reuses of the catalytic system ditopic ligand-CuCl immobilised both in commercial and synthesised [EMIM][OTf]. The study with the complexes with ditopic ligands started with the DiBox and DAX ligands bearing isopropyl substituents (*i*PrDiBox(◆) and *i*PrDAx (▲)) because the synthesis of these ligands is economically more accessible.

The synthesis of DiBox ligands has been previously reported by our research group.[18] These ligands were prepared by condensation of *α,α´*-dibromo-*p*-xylene with two moieties of the corresponding methylene-bridged bis(oxazoline) previously deprotonated with one equivalent of *t*BuOK. Alternatively, DAX ligands were prepared by deprotonation of the corresponding azabis(oxazoline) with butyllitium and subsequent reaction with *α,α'*-dibromo-*p*-xylene.[15,16]

When the reaction was carried out with *i*PrDiBox-CuCl immobilised in commercial [EMIM][OTf] (◆ in Figure 3), it can be seen that during the first two runs the enantioselectivity was low, much more lower in fact than that obtained with the catalytic

complex of *i*PrBox (54% ee *trans*). When the catalyst was recovered the results improved, reaching the same values as with the monotopic ligand. This could indicate that in the first two runs there was free copper left in the reaction medium, *i.e.* not all the copper was complexed with the bis(oxazolines) moieties, so the reaction was partially catalysed in a non-enantioselective way. The recoverability of this catalytic system is good. It is possible to recover it, at least, eight times without an important loss of enantioselectivity.

With *i*PrDAX-CuCl immobilised in commercial [EMIM][OTf] (▲ in Figure 3) there was an important loss of enantioselectivity with regard to the results obtained with *i*PrAzabox-CuCl in the same conditions (57% ee trans). These poor values not only appear during the first two runs, as happened with the *i*PrDiBox ligand, but they are constant during all the catalyst recoveries, being the *trans*-cyclopropanes enantiomeric excess almost null for all uses of the catalyst.

Next, we tested the copper complexes of the ditopic ligands bearing *tert*-butyl groups, also immobilised in commercial [EMIM][OTf] (*t*BuDiBox (■) and *t*BuDAX (●)). When the complex *t*BuDiBox-CuCl immobilised in [EMIM][OTf] was used as catalytic system (■ in Figure 3), similar values were obtained in the first run compared with the values obtained with *t*BuBox-CuCl in the same conditions (34% ee trans, Table 1, entry 2). The enantiomeric excess was also increased in more than 20 units after the second run, similarly to what happened with the *i*PrDiBox ligand. The catalytic system was recovered satisfactorily, being it possible to use it up to eight runs without loss of properties.

With *t*BuDAX-CuCl immobilised in the IL (● in Figure 3) good enantioselective results were obtained, even slightly better than those obtained with the complex *t*BuAzabox-CuCl (85% ee in *trans*-cyclopropanes). The recoverability of the catalyst is possible up to nine runs, but with a progressive decrease in enantioselectivity: in the first run 89% ee was obtained, which decreased to 66% ee in the ninth run.

With regard to the results described before,[11] it is clear that we were not able to obtain an efficient catalytic system, displaying good yields and enantioselectivities and being highly recoverable. As discussed before, the origin of these drawbacks seem to be in the nature of the IL. The synthesis of [EMIM][OTf] has been previously reported,[24,25] so we decided to test again the synthesised IL and immobilise the *t*BuDAX-CuCl complex in it. The results obtained with this catalytic system are also displayed in Figure 3 (✳). As can be seen, the catalytic system could be used up to 14 times with a rather constant and very high enantioselectivity in the major *trans*-cyclopropanes, with %ee values even better than those obtained with the *t*BuAzabox-CuCl complex immobilised in the same IL (89 %ee in *trans*-cyclopropanes). Yields are within the range of 50–92% (67% in the first run and 54% in the 14th run), which are quite good, given that a 1:1 styrene/diazocompound proportion is used and the dimerization of ethyl diazoacetate is competing. Finally, *trans*/*cis* diastereoselectivities are also in the normal range (from 75:25 to 72:28) described for homogeneous catalysis with similar catalytic systems.

2.2 Catalysis in [BMIM][PF_6]

Although the catalytic system *t*BuDAX-CuCl immobilised in the [EMIM][OTf] supplied by Vaultier´s group allows achieving excellent results in cyclopropanation reaction during up to 14 runs, it would be desirable to be able to obtain similar results with a commercially available IL. Davies and co-workers described in 2004 the cyclopropanation reaction of styrene with ethyl diazoacetate using the *t*BuBox-Cu(OTf) complex immobilised in some ILs as catalyst.[22] In particular, excellent results were described with [BMIM][PF_6] (1-butyl-3-methylimidazolium triflate), a IL that they prepared from [BMIM][Cl], so we first tried to reproduce Davies´s results, using the same ligand and IL, but changing the Cu(I) salt from Cu(OTf) to CuCl and using a [BMIM][PF_6] commercially available. We also included other chiral ligands from the Box and Azabox families, in order to find the optimal system. We

started by testing the catalytic systems consisting of monotopic ligand-CuCl complexes immobilised in [BMIM][PF_6]. The corresponding results are gathered in Table 2.

Table 2. Cyclopropanation reaction of styrene with ethyl diazoacetate catalysed by monotopic ligand-CuCl complexes immobilised in [BMIM][PF_6].[a]

Entry	Ligand	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1[b]	*t*BuBox (**1d**)	47	75/25	95	91
2	*i*PrBox (**1c**)	51	65/35	87	62
3	*t*BuBox (**1d**)	63	72/28	98	87
4	PhBox (**1e**)	56	74/26	70	48
5	InBox (**1f**)	52	56/44	78	78
6	*i*PrAzabox (**1a**)	43	62/38	56	45
7	*t*BuAzabox (**1b**)	56	74/26	97	82

[a] Reagents and conditions: styrene (1 equiv.), ethyl diazoacetate (1 equiv.), L*-CuCl (1 mol%), [BMIM][PF_6] 0.5 mL, room temperature, 20h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1*R*,2*R*)-*trans*-cyclopropane and (1*R*,2*S*)-*cis*-cyclopropane are the major isomers. [b] Taken from ref. [22].

As we can see in Table 2, the immobilisation of the Box-CuCl and Azabox-CuCl complexes in [BMIM][PF_6] leads to good results in all cases. With *t*BuBox-CuCl (entry 3) it is possible to obtain excellent enantioselectivity results, which are comparable to those described by Davies (entry 1). As happened when the complex was immobilised in [EMIM][OTf], the best results are obtained when the chiral ligand bears *tert*-butyl groups (entries 3 and 7). In view of the good results obtained with this commercial IL, CuCl complexes of the analogous ditopic ligands were tested in the same conditions. The results of these experiments (%ee in *trans*-cyclopropanes) are represented in Figures 4 and 5.

We first tested the cyclopropanation reaction with the complexes DiBox-CuCl immobilised in commercial [BMIM][PF_6]. Figure 4 displays the catalytic results obtained in successive recoveries of these catalytic systems. Again, the %ee in *trans*-cyclopropanes was chosen as the most interesting result to represent the performance of the catalysts.

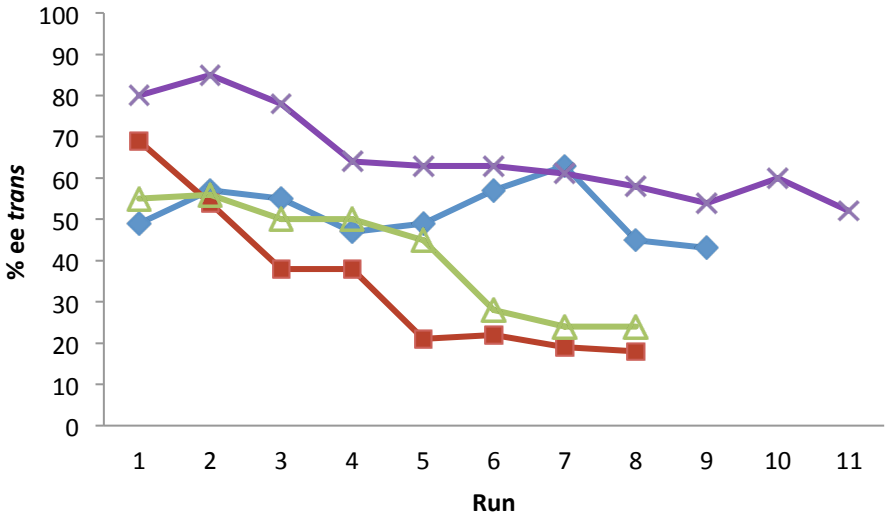


Figure 4. Recycling experiments with the complexes DiBox-CuCl immobilised in [BMIM][PF_6]. *i*PrDiBox (**2c**) (◆), *t*BuDiBox (**2d**) (■), PhDiBox (**2e**) (△), InDiBox (**2f**) (✕).

A general overview of the graph allows concluding that there is a progressive loss of enantioselectivity along the reuses of all catalytic systems, which is more pronounced in the case of *t*BuDiBox-CuCl (**2d**) (■). Except for InDiBox-CuCl (**2f**) (✕), in all cases the enantioselectivity obtained in *trans*-cyclopropanes, even in the first run, is lower than that obtained with the analogous complexes with monotopic ligands (Table 2). The results obtained with InDiBox-CuCl (**2f**) (✕) immobilised in [BMIM][PF_6] are the best in this series of experiments, and it is possible to carry out the cyclopropanation reaction up to 11 times. During the first three runs there is not any loss of enantioselectivity, and in the rest only a slight decrease is observed.

The yield obtained with all the complexes is around 50%, a good result given that the reaction was carried out in a 1/1 equivalent of the reactants as we have previously commented. The *trans/cis* ratio is somewhat lower than the typical values obtained for this reaction (*ca.* 70/30). A diastereoselectivity around 55/45 was obtained in all cases, except in the case of the complex with the PhDiBox (**2e**) ligand, which was slightly higher (64/36). This behaviour is

related to the presence of the benzyl group in the bis(oxazoline) bridge, and had already been reported in the case of dibenzylated *t*BuBox ligands.[26]

As we have just seen, the use of the DiBox ligands resulted in a continuous decrease in the enantioselectivity values upon recovery. This is probably due to a loss of ligand along the successive catalyst recoveries, by extraction of the IL phase with the organic solvent (hexane). DAX ligands have proven to be much more coordinating with copper, so it should be more difficult to extract them from the IL phase during the catalyst recovery procedure, thereby avoiding loss of enantioselectivity throughout successive runs. The results of the corresponding experiments carried out with DAX-CuCl complexes immobilised in [BMIM][PF_6] are shown in Figure 5.

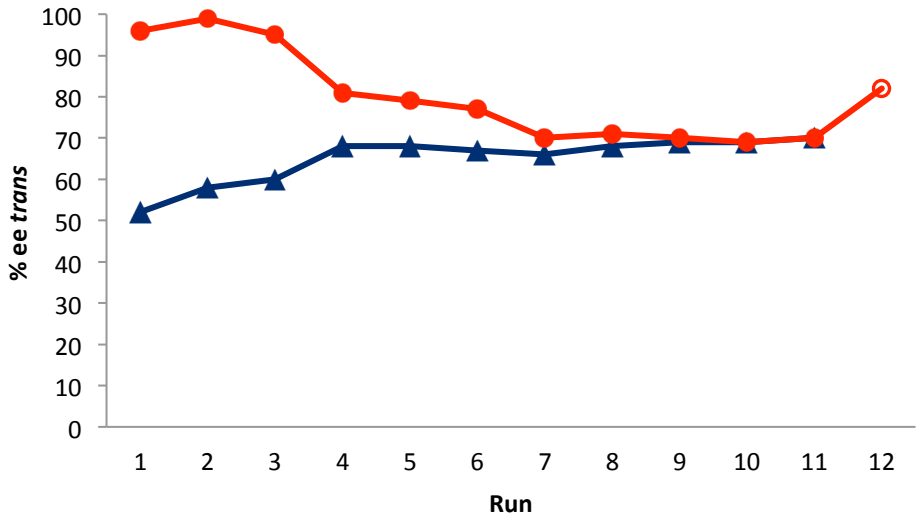


Figure 5. Recycling experiments with the complexes DAX-CuCl immobilised in [BMIM][PF_6]. *i*PrDAX (**2a**) (▲), *t*BuDAX (**2b**) (●).

As can be seen in Figure 5, using both DAX ligands the decline in enantioselectivity is less pronounced than in the case of complexes with DiBox ligands. In the case of the complex of *i*PrDAX (**2a**) (▲), we can even observe a slight improvement in enantioselectivity along recoveries. As stated above, the explanation for this could be the presence of free copper in

the reaction medium at the beginning of the catalytic runs. The values obtained during all the cycles were similar to that obtained with the *i*PrAzabox-CuCl complex in the same conditions (Table 2, entry 6) indicating a very good recovery of this catalytic system.

With the complex of *t*BuDAX (**2b**) (●) immobilised in the commercial IL [BMIM][PF_6] the enantioselectivity results in *trans*-cyclopropanes are close to 100% over the first three runs. Then, a slight decrease in enantioselectivity is observed, probably due to a loss of chiral ligand during the catalyst recovery. To verify this hypothesis an additional 0.25% mol of *t*BuDAX ligand was added in the 12th run, and, as can be observed in Figure 5 (○), an improvement in the enantioselectivity was immediately obtained.

With these two DAX ligands, yields were also maintained in a range of 50-65%. Finally, *trans*/*cis* diastereoselectivities were also in the normal range described for homogeneous catalysis with similar catalytic systems (around 70/30 for both DAX ligands).

3. Conclusion

Two main conclusions arise from the results described in the present work. First, the nature of the ionic liquid used to immobilise the catalytic complex is determinant both for the results of the reaction (yield and enantioselectivities) and for the recovery of the catalyst. Commercial [EMIM][OTf] was completely inadequate to prepare recoverable catalytic phases for the cyclopropanation reaction, catalysed by copper complexes of both monotopic and ditopic chiral ligands. On the other hand, the same IL obtained by published synthetic procedures, displayed much better performance, allowing at least 14 uses of the *t*BuDAX-CuCl catalyst with excellent results. Commercial [BMIM][PF_6] exhibits better behaviour than [EMIM][OTf], but the best results obtained with this IL and the copper complexes with ditopic ligands are still far from those obtained with the synthesised [EMIM][OTf].

The second main conclusion is that, contrary to our starting hypothesis, the use of bis-copper complexes of ditopic ligands does not seem to suppose an advantage to improve the

recoverability of the catalytic IL phases. A continuous decrease in enantioselectivity, most probably due to partial extraction of free ligand during the reaction work-up, is also observed with these kinds of complexes. In this sense, catalytic IL phases of complexes of conventional monotopic ligands perform equal or even better than those of ditopic ligands.

4. Experimental

4.1. General

All reactions were carried out under argon atmosphere in oven-dried glassware. All the reagents and solvents were commercially available. ILs were purchased from Sigma-Aldrich. Anhydrous solvents such as dichloromethane and *n*-hexane were obtained from an SPS-device. Ionic liquids were stored under vacuum in presence of P_2O_5, the other reactants were used as received without further purification. Chiral ligands were synthesised according to literature procedures.[15,16,18]

4.2. Catalyst immobilisation in ionic liquids using monotopic ligands

A solution of CuCl (3.76 mg, 0.038 mmol) and the corresponding monotopic ligand (0.02 mmol) in the corresponding IL (0.5mL) was stirred at room temperature until a clear pale green solution was obtained.

Alternatively, the catalyst immobilisation was realized as follows: A solution of CuCl (3.76 mg, 0.038 mmol) and the corresponding monotopic ligand (0.04 mmol) in 2 mL of anhydrous dichloromethane was stirred at room temperature for 30 minutes. Then, the mixture was microfiltered to eliminate the remaining CuCl. Afterwards, 0.5 mL of the corresponding IL was added and the mixture was stirred for 15 min. Next, the dichloromethane was removed under vacuum.

4.3. Catalyst immobilisation in ionic liquids using ditopic ligands

The immobilisation of complexes with ditopic ligands in IL was realized in the same way as commented in 4.2 for monotopic ligands.

4.4. General procedure for the cyclopropanation reaction

To the complex immobilised in the ionic liquid solution under Ar atmosphere, styrene (3.8 mmol) was added. Then, ethyl diazoacetate (3.8 mmol) was slowly added (3 h) using a syringe pump. The reaction mixture was stirred at room temperature for 20 h. After this time the products were extracted with hexane (3×3 mL), and *n*-decane (100 mg) was added to the hexane solution as an internal standard for the GC analysis. The remaining solution of the catalyst in the IL was dried and reused following the same method.

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Asymmetric cyclopropanation in Ionic Liquids promoted by dicopper complexes of ditopic ligands

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Supporting Information

Table 1. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by Cu-iPrBox and Cu-iPrDiBox in commercial [EMIM][OTf].[a]

Entry	Ligand	Run	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1	iPrBox	--	29	70/30	54	57
2	iPrDiBox	1	25	61/39	29	54
3		2	25	58/42	27	50
4		3	25	61/39	42	50
5		4	43	59/41	43	50
6		5	66	57/43	46	50
7		6	57	57/43	40	47
8		7	45	57/43	39	45
9		8	59	57/43	44	44

[a] Reagents and conditions: styrene (1 equiv.), ethyl diazo-acetate (1 equiv.), L*-CuCl (1 mol%), EMIM[OTf] 0.5 mL, room temperature, 20h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1R,2R)-trans-cyclopropane and (1R,2S)-cis-cyclopropane are the major isomers.

Table 2. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by Cu-tBuBox and Cu-tBuDiBox in commercial [EMIM][OTf]. [a]

Entry	Ligand	Run	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1	tBuBox	--	29	72/28	68	72
2	tBuDiBox	1	32	66/34	41	56
3		2	29	63/37	62	52
4		3	43	63/37	67	52
5		4	39	69/31	71	56
6		5	59	67/33	67	55
7		6	53	67/33	65	53
8		7	53	67/33	59	51
9		8	68	65/35	60	51

[a] Reagents and conditions: styrene (1 equiv.), ethyl diazo-acetate (1 equiv.), L*-CuCl (1 mol%), EMIM[OTf] 0.5 mL, room temperature, 20h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1R,2R)-trans-cyclopropane and (1R,2S)-cis-cyclopropane are the major isomers.

Table 3. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by Cu-iPrAzaBox and Cu-iPrDAX in commercial [EMIM][OTf]. [a]

Entry	Ligand	Run	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1	iPrAzaBox	--	17	65/35	57	49
2	iPrDAX	1	17	62/38	15	56
3		2	21	64/36	2	23
4		3	30	62/38	7	23
5		4	44	62/38	4	24
6		5	65	60/40	8	22
7		6	52	59/41	6	23
8		7	67	58/42	7	23
9		8	50	58/42	5	21

[a] Reagents and conditions: styrene (1 equiv.), ethyl diazo-acetate (1 equiv.), L*-CuCl (1 mol%), EMIM[OTf] 0.5 mL, room temperature, 20h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1R,2R)-trans-cyclopropane and (1R,2S)-cis-cyclopropane are the major isomers.

Table 4. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by Cu-tBuAzaBox and Cu-tBuDAX in commercial [EMIM][OTf]. [a]

Entry	Ligand	Run	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1	tBuAzaBox	--	28	74/26	85	71
2	tBuDAX	1	22	72/28	89	76
3		2	42	71/29	83	66
4		3	43	70/30	71	60
5		4	51	66/34	68	58
6		5	51	66/34	71	60
7		6	52	65/35	67	61
8		7	57	66/34	67	63
9		8	47	66/34	67	62
10		9	59	65/35	66	63

[a] Reagents and conditions: styrene (1 equiv.), ethyl diazo-acetate (1 equiv.), L*-CuCl (1 mol%), EMIM[OTf] 0.5 mL, room temperature, 20h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1R,2R)-trans-cyclopropane and (1R,2S)-cis-cyclopropane are the major isomers.

Table 5. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by Cu-tBuAzaBox and Cu-tBuDAX in synthesised [EMIM][OTf]. [a]

Entry	Ligand	Run	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1	tBuAzaBox	--	62	73/27	89	82
2	tBuDAX	1	67	75/25	96	88
3		2	88	74/26	97	89
4		3	93	73/27	96	89
5		4	92	73/27	98	89
6		5	63	73/27	97	89
7		6	51	72/28	95	89
8		7	50	73/28	95	89
9		8	53	73/27	95	89
10		9	49	73/27	96	89
11		10	52	73/27	96	89
12		11	51	73/27	95	90
13		12	48	72/28	97	89
14		13	53	73/27	97	88
15		14	54	73/27	96	88

[a] Reagents and conditions: styrene (1 equiv.), ethyl diazo-acetate (1 equiv.), L*-CuCl (1 mol%), EMIM[OTf] 0.5 mL, room temperature, 20h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1R,2R)-trans-cyclopropane and (1R,2S)-cis-cyclopropane are the major isomers.

Table 6. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by Cu-iPrBox and Cu-iPrDiBox in commercial [BMIM][PF6]. [a]

Entry	Ligand	Run	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1	iPrBox	--	51	65/35	87	62
2	iPrDiBox	1	37	55/45	49	56
3		2	58	56/44	57	55
4		3	54	55/45	55	54
5		4	61	56/44	47	53
6		5	52	55/45	49	53
7		6	45	55/45	57	51
8		7	58	56/44	63	46
9		8	53	56/44	45	45
10		9	49	56/44	43	42

[a] Reagents and conditions: styrene (1 equiv.), ethyl diazo-acetate (1 equiv.), L*-CuCl (1 mol%), [BMIM][PF_6] 0.5 mL, room temperature, 20h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1R,2R)-trans-cyclopropane and (1R,2S)-cis-cyclopropane are the major isomers.

Table 7. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by Cu-tBuBox and Cu-tBuDiBox in commercial [BMIM][PF6]. [a]

Entry	Ligand	Run	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1	tBuBox	--	63	72/28	98	87
2	tBuDiBox	1	35	48/52	69	57
3		2	59	51/49	54	52
4		3	69	50/50	38	39
5		4	55	51/49	38	36
6		5	53	51/49	21	34
7		6	53	51/49	22	33
8		7	56	51/49	19	32
9		8	54	52/48	18	29

[a] Reagents and conditions: styrene (1 equiv.), ethyl diazo-acetate (1 equiv.), L*-CuCl (1 mol%), [BMIM][PF_6] 0.5 mL, room temperature, 20h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1R,2R)-trans-cyclopropane and (1R,2S)-cis-cyclopropane are the major isomers.

Table 8. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by Cu-PhBox and Cu-PhDiBox in commercial [BMIM][PF6]. [a]

Entry	Ligand	Run	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1	PhBox	--	56	74/26	70	48
2	PhDiBox	1	44	70/30	55	47
3		2	58	67/33	56	43
4		3	54	66/34	50	38
5		4	54	64/36	50	34
6		5	58	63/37	45	30
7		6	54	62/38	28	32
8		7	57	62/38	24	26
9		8	59	61/39	24	25

[a] Reagents and conditions: styrene (1 equiv.), ethyl diazo-acetate (1 equiv.), L*-CuCl (1 mol%), [BMIM][PF_6] 0.5 mL, room temperature, 20h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1R,2R)-trans-cyclopropane and (1R,2S)-cis-cyclopropane are the major isomers.

Table 9. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by Cu-InBox and Cu-InDiBox in commercial [BMIM][PF6].[a, b]

Entry	Ligand	Run	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1	InBox	--	52	56/44	-78	-78
2	InDiBox	1	51	50/50	-80	-85
3		2	50	49/51	-85	-84
4		3	52	49/51	-78	-83
5		4	37	56/44	-64	-73
6		5	59	49/51	-63	-70
7		6	59	50/50	-63	-72
8		7	54	52/48	-61	-69
9		8	55	52/48	-58	-68
10		9	56	52/48	-54	-63
11		10	63	52/48	-60	-62
12		11	59	52/48	-52	-57

[a] Reagents and conditions: styrene (1 equiv.), ethyl diazo-acetate (1 equiv.), L*-CuCl (1 mol%), [BMIM][PF_6] 0.5 mL, room temperature, 20h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1R,2R)-trans-cyclopropane and (1R,2S)-cis-cyclopropane are the major isomers. [b] The absolute configuration of the ligand is the contrary so we obtain that (1*S*,2*S*)-*trans*-cyclopropane and (1*S*,2*R*)-*cis*-cyclopropane are the major isomers. It is highlighted with the negative sign.

Table 10. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by Cu-iPrAzaBox and Cu-iPrDAX in commercial [BMIM][PF6]. [a]

Entry	Ligand	Run	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1	iPrAzaBox	--	43	62/38	56	45
2	iPrDAX	1	40	61/39	52	49
3		2	58	62/38	58	49
4		3	59	64/36	60	50
5		4	65	65/35	68	51
6		5	62	65/35	68	51
7		6	54	66/34	67	53
8		7	56	67/33	66	53
9		8	52	66/34	78	56
10		9	60	67/33	69	56
11		10	47	72/28	69	57
12		11	59	65/35	70	58

[a] Reagents and conditions: styrene (1 equiv.), ethyl diazo-acetate (1 equiv.), L*-CuCl (1 mol%), [BMIM][PF_6] 0.5 mL, room temperature, 20h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1R,2R)-trans-cyclopropane and (1R,2S)-cis-cyclopropane are the major isomers.

Table 11. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by Cu-tBuAzaBox and Cu-tBuDAX in commercial [BMIM][PF6]. [a]

Entry	Ligand	Run	Yield (%)	*Trans/cis*	%ee *trans*	%ee *cis*
1	tBuAzaBox	--	56	74/26	97	82
2	tBuDAX	1	30	72/28	96	87
3		2	36	72/28	99	81
4		3	44	72/28	95	76
5		4	52	70/30	81	72
6		5	51	68/32	79	69
7		6	54	67/33	77	67
8		7	50	67/33	70	65
9		8	46	66/34	71	65
10		9	53	66/34	70	65
11		10	30	63/37	69	63
12		11	55	65/35	70	66
13[b]		12	67	69/31	82	75

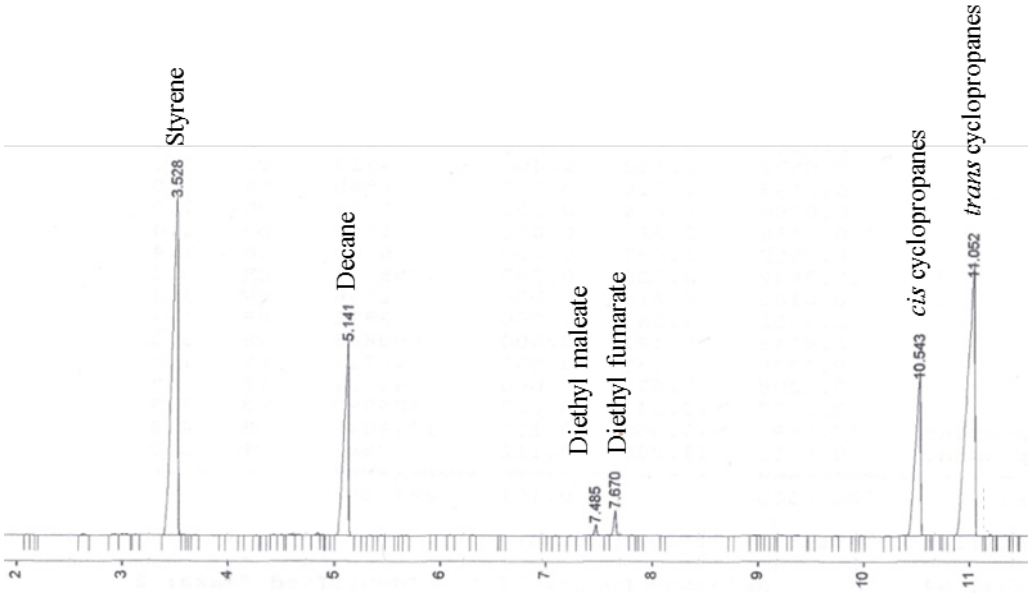
[a] Reagents and conditions: styrene (1 equiv.), ethyl diazo-acetate (1 equiv.), L*-CuCl (1 mol%), [BMIM][PF_6] 0.5 mL, room temperature, 20h. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1R,2R)-trans-cyclopropane and (1R,2S)-cis-cyclopropane are the major isomers. [b] 0,25% mol of tBuDAX was added to the catalytic system.

Gas chromatography analyses of the Cyclopropanation reaction of styrene with ethyl diazoacetate:

FID from Hewlett–Packard 5890-II, cross-linked methyl silicone column (SPB): 25m ×0.2mm × 0.33μm; helium as carrier gas. 20 psi; injector temperature: 230 °C; detector temperature: 250 °C; oven program: 70 °C (3 min), 15°C min^{-1} to 200 °C (5 min); retention times: ethyl diazoacetate 3.2 min, styrene 3.5 min, *n*-decane 5.1 min, diethylmaleate 7.4 min, diethyl fumarate 7.6 min, *cis* cyclopropanes 10.5 min, *trans* cyclopropanes 11.0 min.

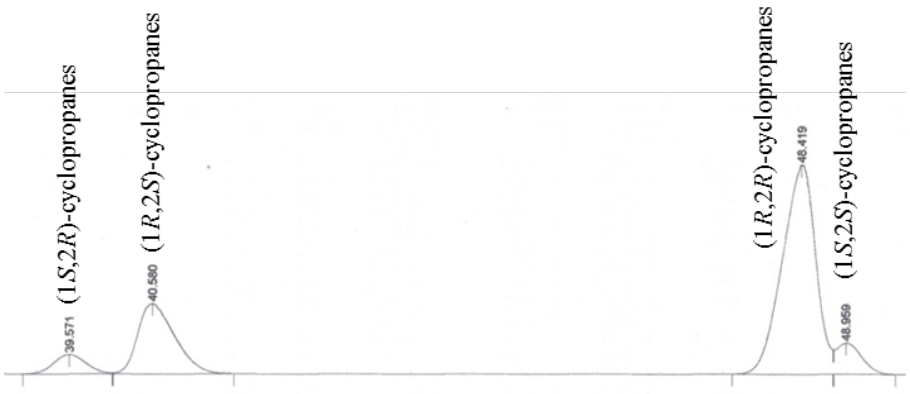
In order to determine the cyclopropanation yield *n*-decane is used as internal standard. A calibration curve was done previously in the group to calibrate the FID response of the products.

$$\%\ Yield = 0.8153\ \frac{decane\ mmol \cdot cyclopropanes\ area}{diazoacetate\ mmol \cdot decane} \cdot 100$$



Typical CG chromatogram for the cyclopropanation reaction of styrene and ethyl diazoacetate.

The enantioselectivities of the reactions were also determined by gas chromatography: FID from Hewlett–Packard 5890-II, Cyclodex-*β* column: 30 m x 0,25 mm x 0,25 µm; helium as carrier gas. 20 psi; injector temperature: 230 °C; detector temperature: 250 °C; oven temperature program: 120 °C isotherm; retention times: (1*S*,2*R*)-cyclopropane 39.6 min, (1*R*,2*S*)-cyclopropane 40.6 min, (1*R*,2*R*)-cyclopropane 48.3 min, (1*S*,2*S*)-cyclopropane 48.9 min.



Typical chiral CG chromatogram for the cyclopropanation reaction of styrene and ethyl diazoacetate.